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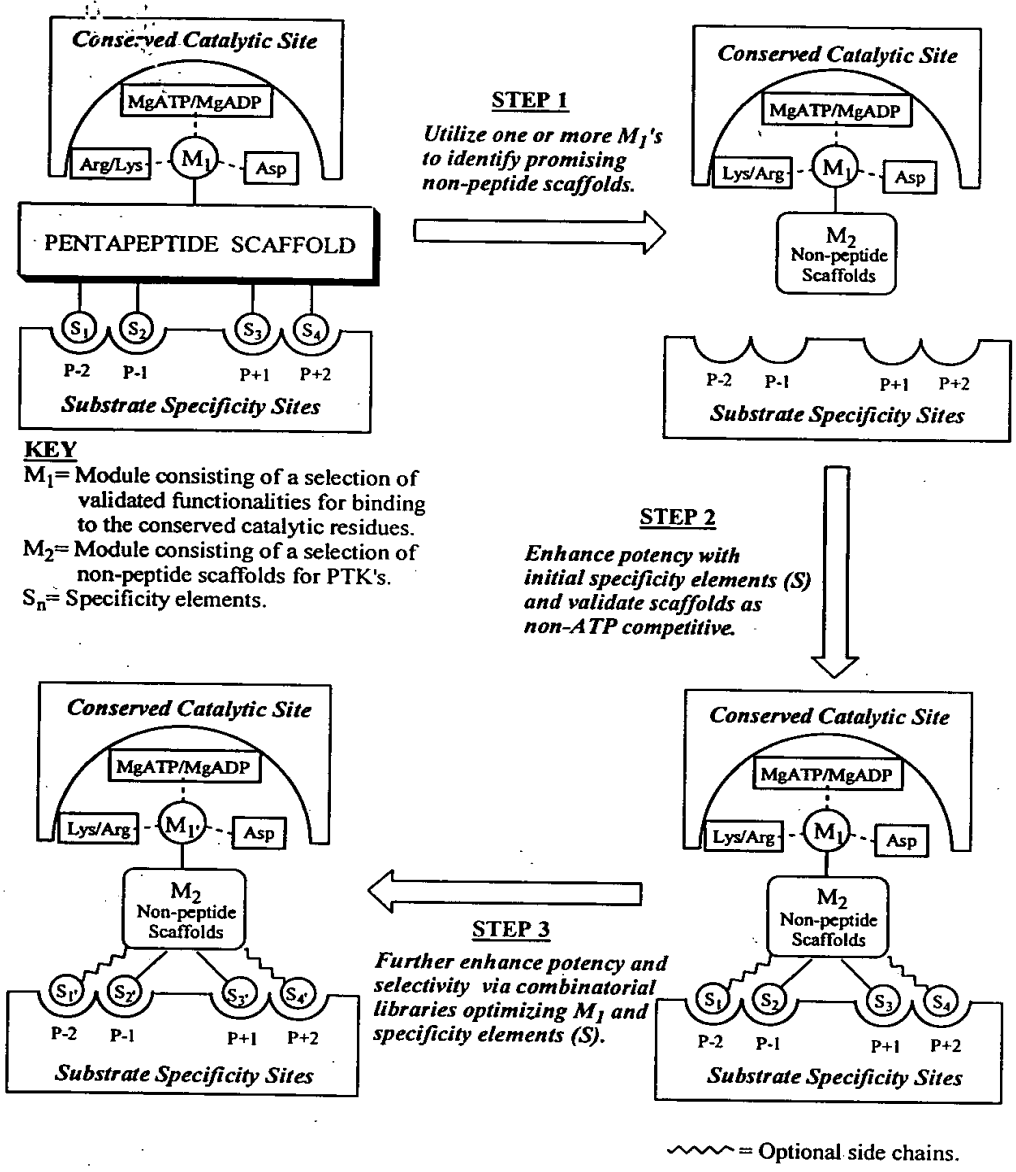
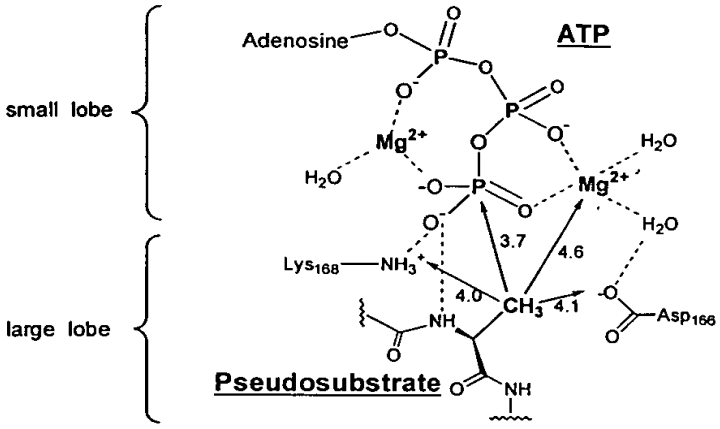
Figure 1

MODULAR STRATEGY FOR DEVELOPING NON-PEPTIDE PROTEIN KINASE INHIBITORS



Figur 2
x-ray structur of (PKA):Mg_2ATP:pseudosubstrat inhibitor



(Distances in Å)

In Closed Conformation

Figure 3

General Module M_1 Design Features For Binding To The Conserved Protein Kinase Catalytic Region

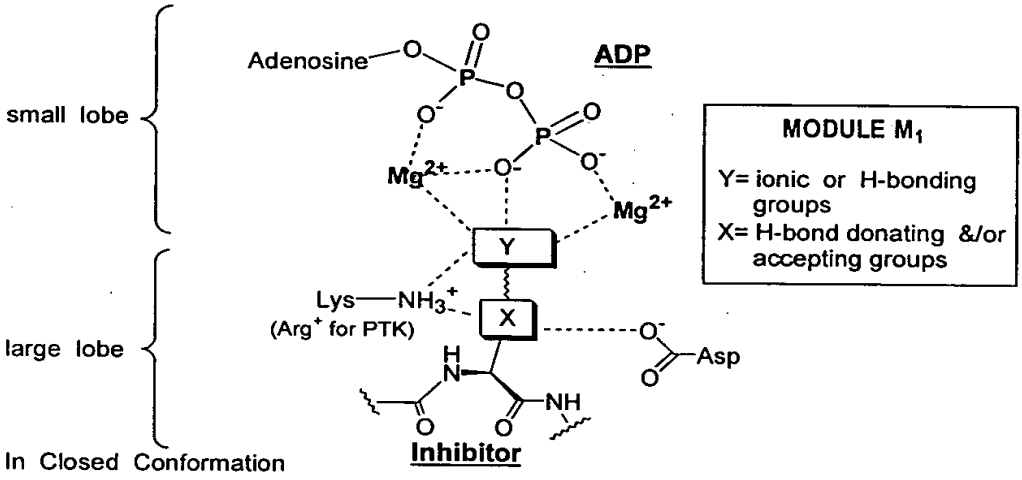


Figure 4

SUBSTRATE BEHAVIOR FOR BORONIC ACID PKA INHIBITORS 21 & 22

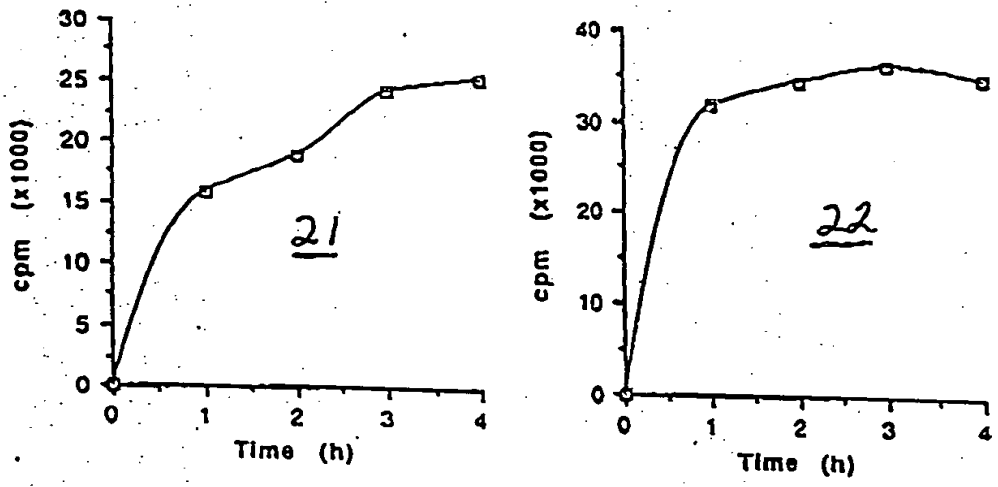


Figure 5

Binding interactions of src substrate Ac-Ile-Tyr-Gly-Glu-Phe-NH_2 in model src active site.

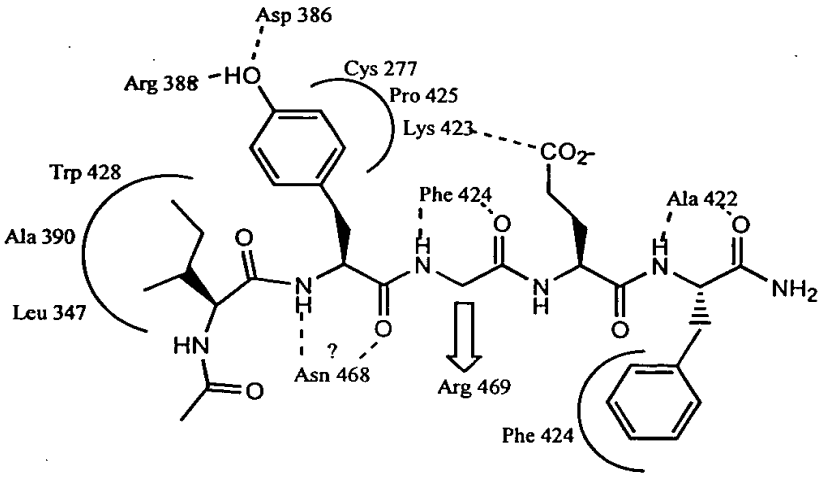
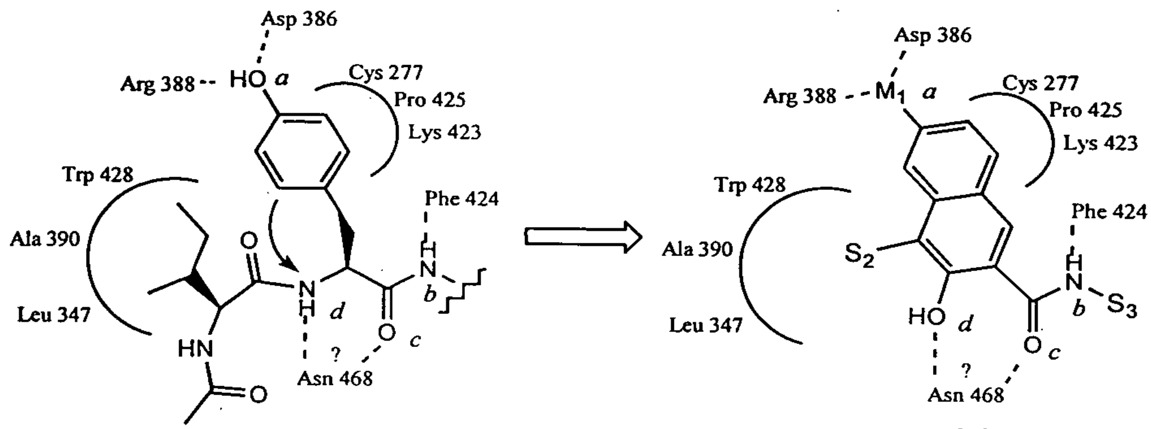


Figure 6

Design of naphthalene-based src inhibitor scaffold

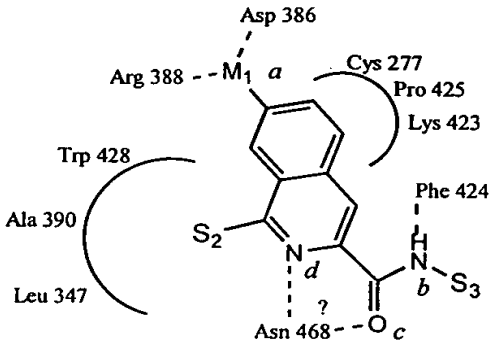


src:peptide substrate complex

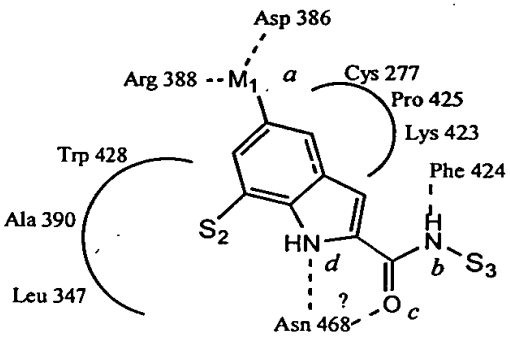
src:naphthalene-based non-peptide inhibitor binding mode

Figure 7

Design of isoquinoline and indole-based src inhibitor scaffolds



src:isoquinoline-based non-peptide inhibitor binding mode



src:indole-based non-peptide inhibitor binding mode

Figure 8

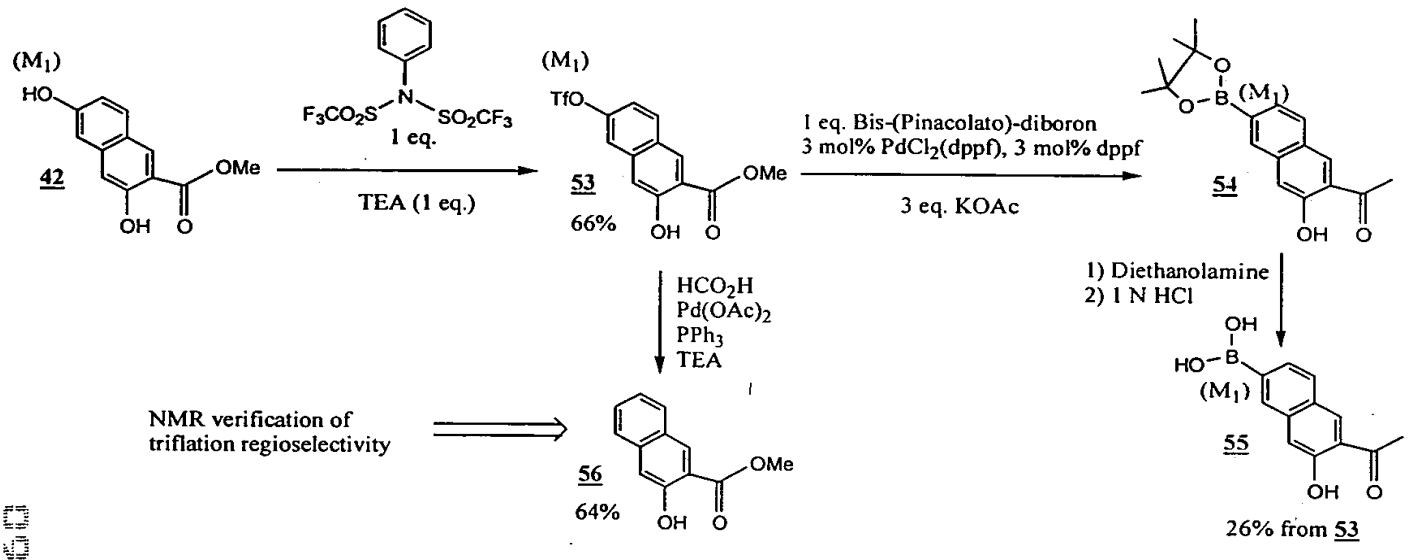

(M1)
HO
42
OMe
OH
O
F3CO2S
N
SO2CF3
1 eq.
TEA (1 eq.)
(M1)
TfO
53
66%
OMe
OH
O
1 eq. Bis-(Pinacolato)-diboron
3 mol% PdCl2(dppf), 3 mol% dppf
3 eq. KOAc
(M1)
54
OH
O
1) Diethanolamine
2) 1 N HCl
OH
HO
B
(M1)
55
OH
O
26% from 53
HCO2H
Pd(OAc)2
PPh3
TEA
NMR verification of
triflation regioselectivity
56
64%
OMe
OH
O

Figure 9

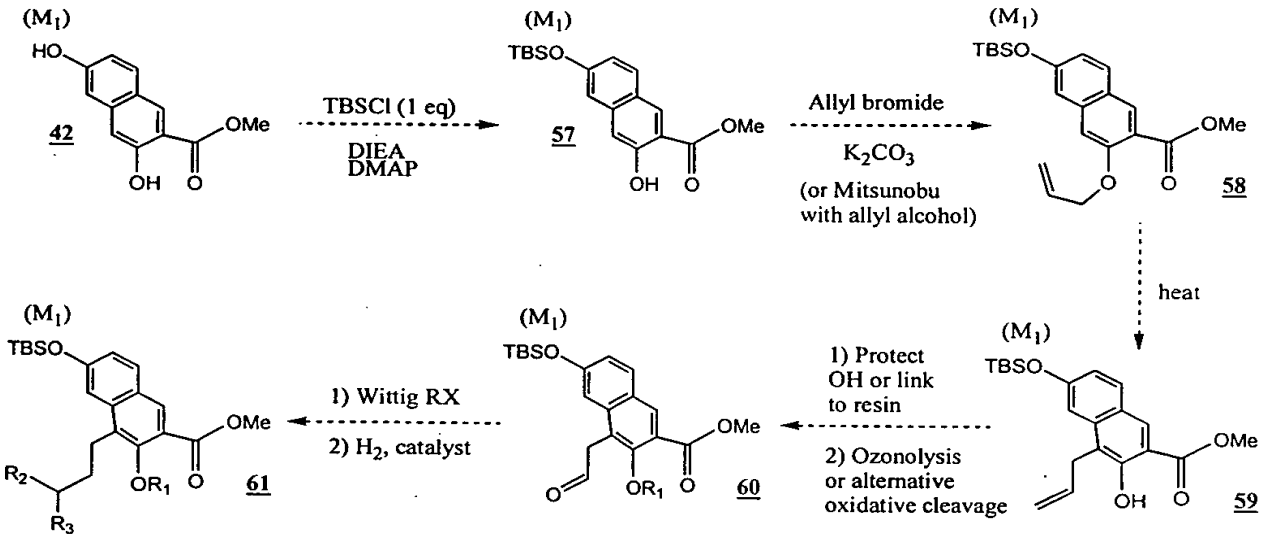

(M1)
HO
42
OMe
OH
O
TBSCl (1 eq)
DIEA
DMAP
(M1)
TBSO
57
OMe
OH
O
Allyl bromide
K2CO3
(or Mitsunobu
with allyl alcohol)
(M1)
TBSO
OMe
O
O
58
heat
(M1)
TBSO
OMe
OH
O
59
1) Protect
OH or link
to resin
2) Ozonolysis
or alternative
oxidative cleavage
(M1)
TBSO
OMe
OR1
O
O
60
1) Wittig RX
2) H2, catalyst
(M1)
TBSO
OMe
R2
OR1
O
R3
61

Figure 10

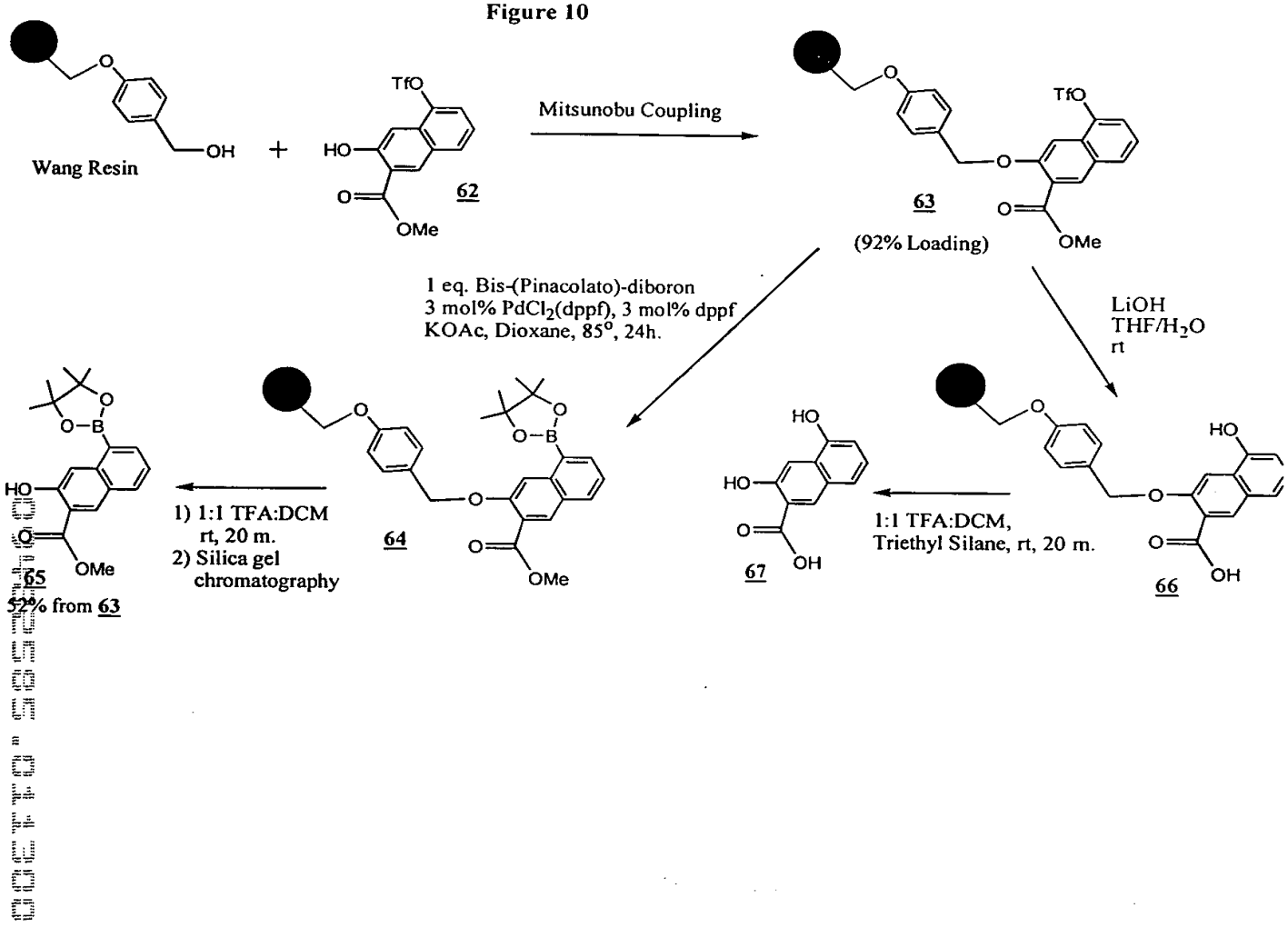

Wang Resin
OH
TfO
HO
OMe
62
Mitsunobu Coupling
63
(92% Loading)
1 eq. Bis-(Pinacolato)-diboron
3 mol% PdCl2(dppf), 3 mol% dppf
KOAc, Dioxane, 85°, 24h.
LiOH
THF/H2O
rt
64
1) 1:1 TFA:DCM
rt, 20 m.
2) Silica gel
chromatography
65
52% from 63
1:1 TFA:DCM,
Triethyl Silane, rt, 20 m.
67
66
OH

Figure 11

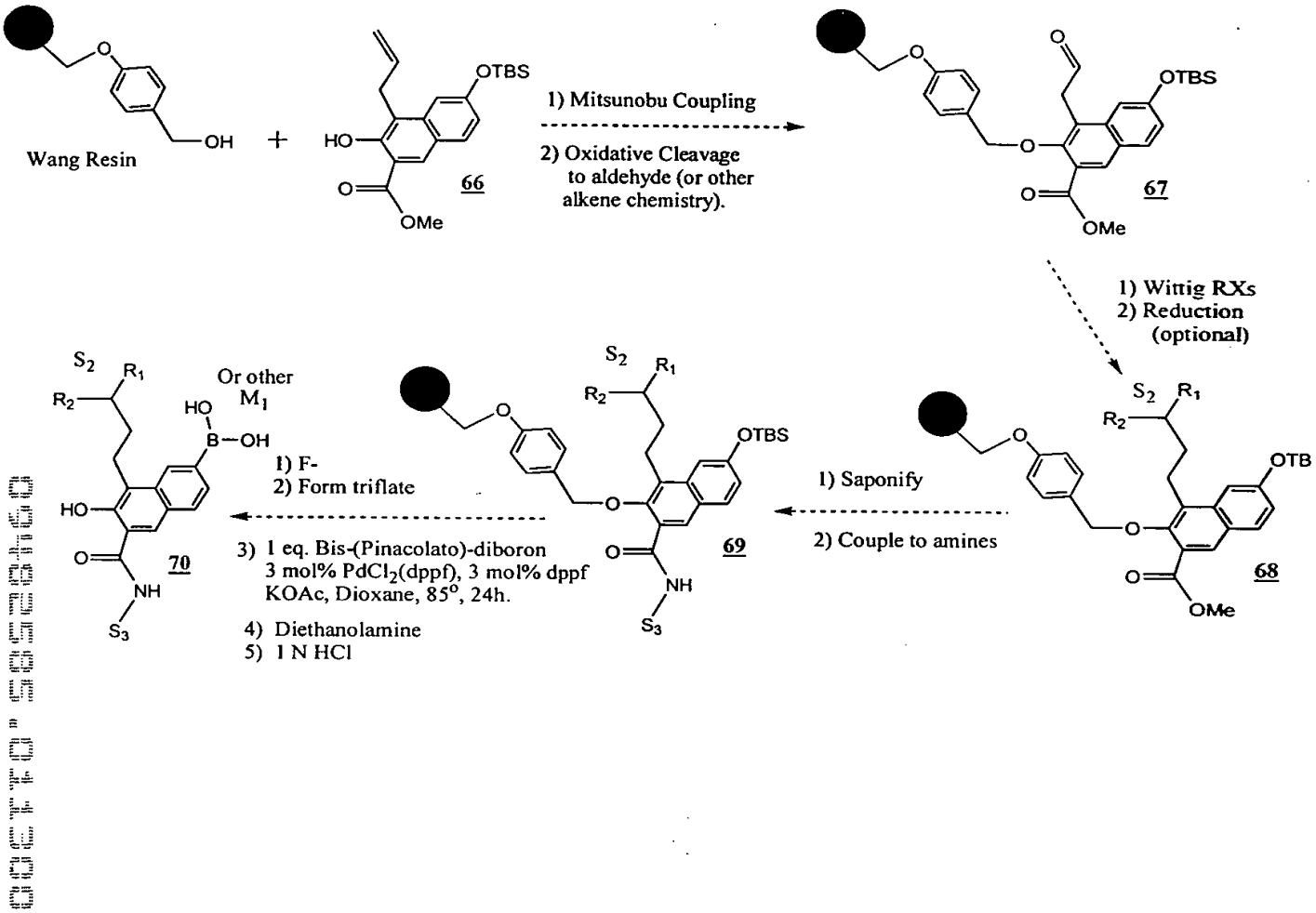

Wang Resin
OH
HO
OTBS
O
OMe
66
1) Mitsunobu Coupling
2) Oxidative Cleavage to aldehyde (or other alkene chemistry).
67
1) Wittig RXs
2) Reduction (optional)
68
1) Saponify
2) Couple to amines
69
3) 1 eq. Bis-(Pinacolato)-diboron
3 mol% PdCl2(dppf), 3 mol% dppf
KOAc, Dioxane, 85°, 24h.
4) Diethanolamine
5) 1 N HCl
1) F-
2) Form triflate
Or other M1
B—OH
70
S2
R1
R2
NH
S3

Figure 12

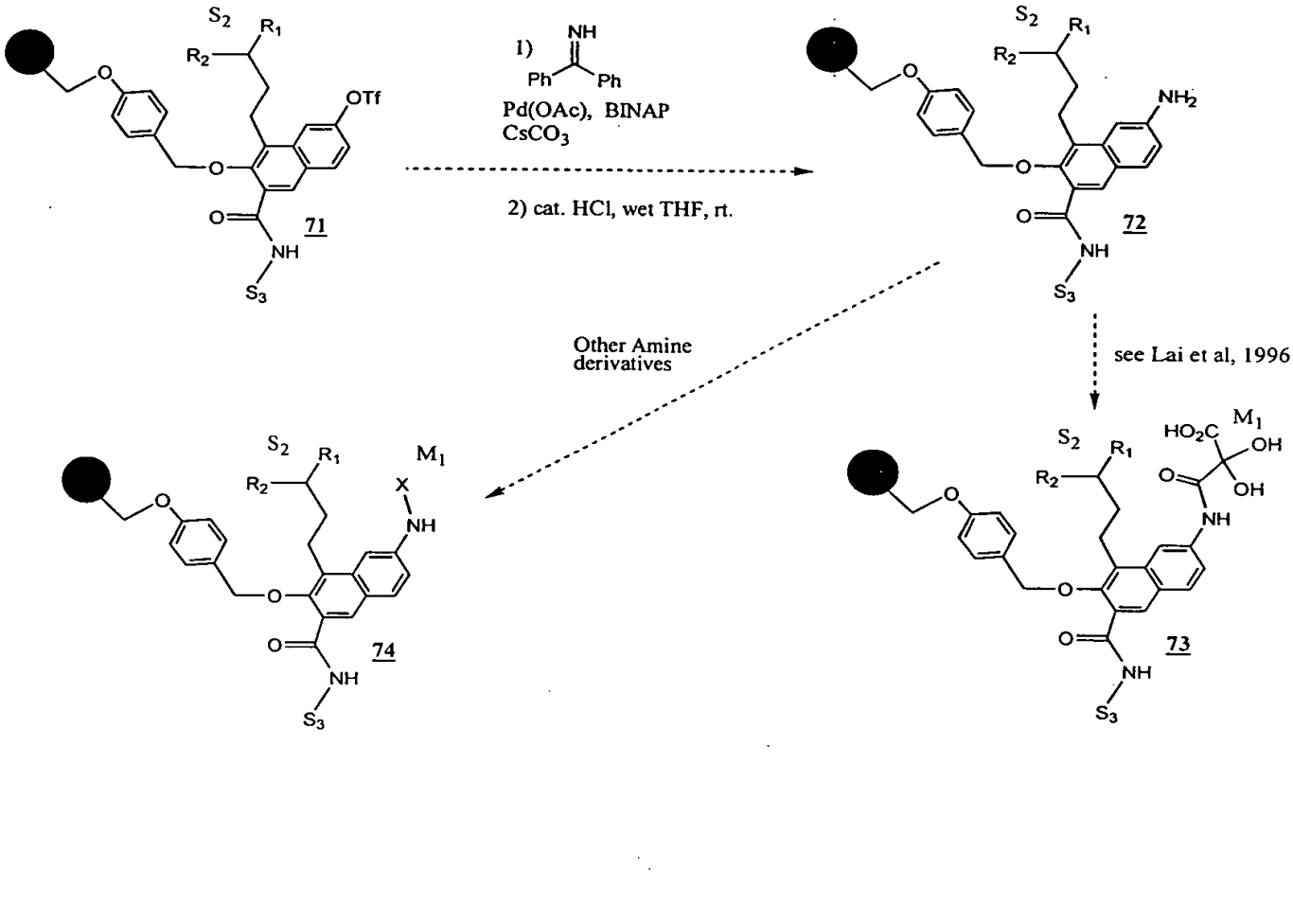

S2
R1
R2
OTf
O
O
O
NH
S3
71
1)
NH
Ph
Ph
Pd(OAc), BINAP
CsCO3
2) cat. HCl, wet THF, rt.
NH2
72
Other Amine derivatives
see Lai et al, 1996
M1
X
74
HO2C
OH
OH
73

Figure 13

(Residues are from the IRTK ternary structure and dotted bonds are H-bonds)

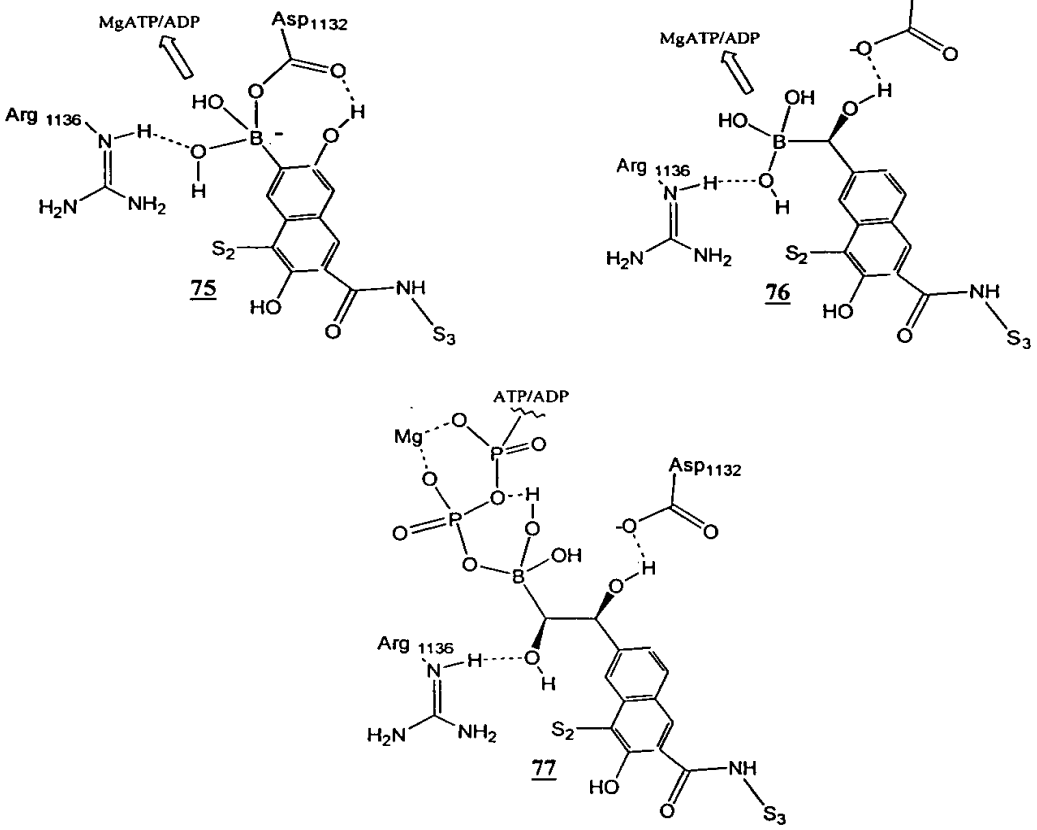


FIGURE 14

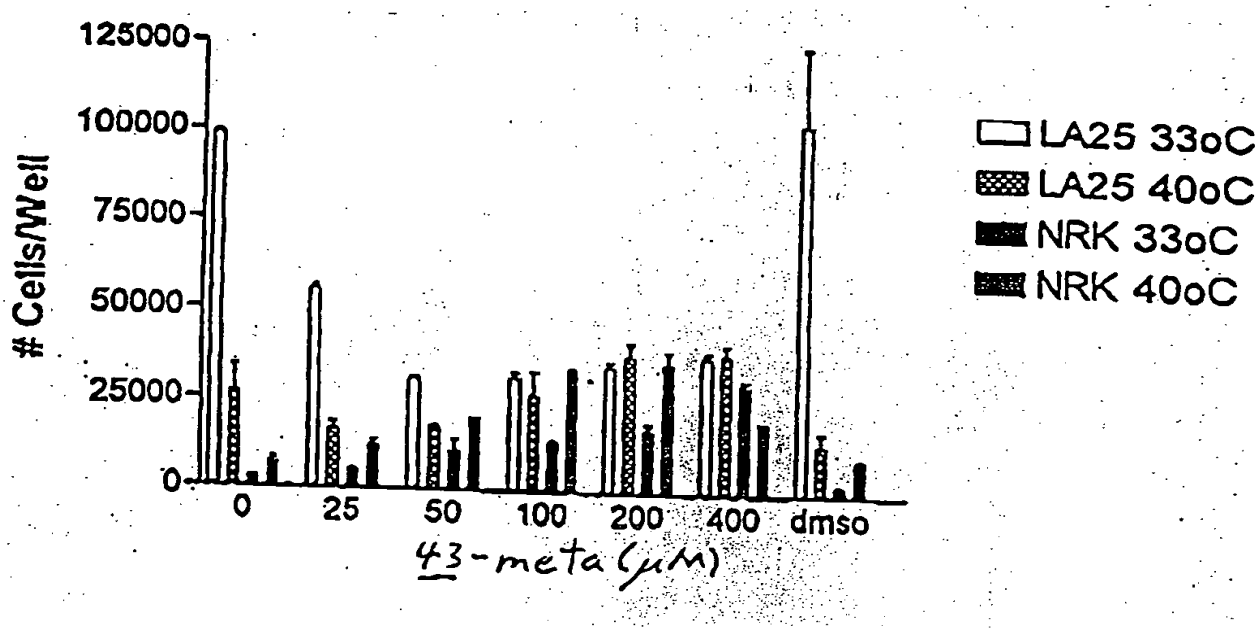


FIGURE 15A

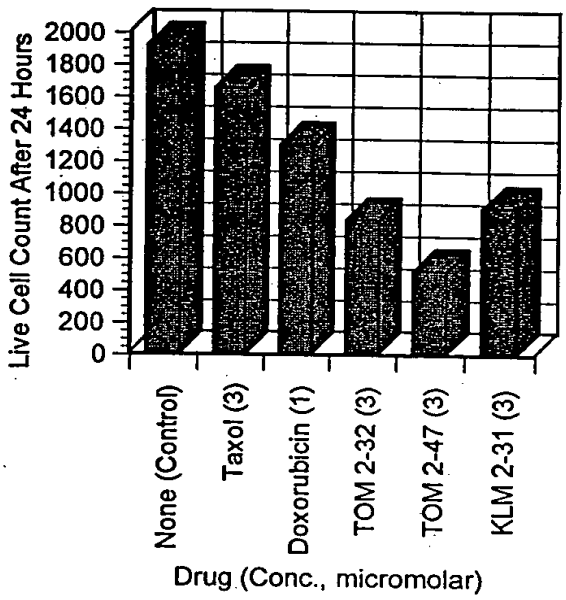


FIGURE 15B

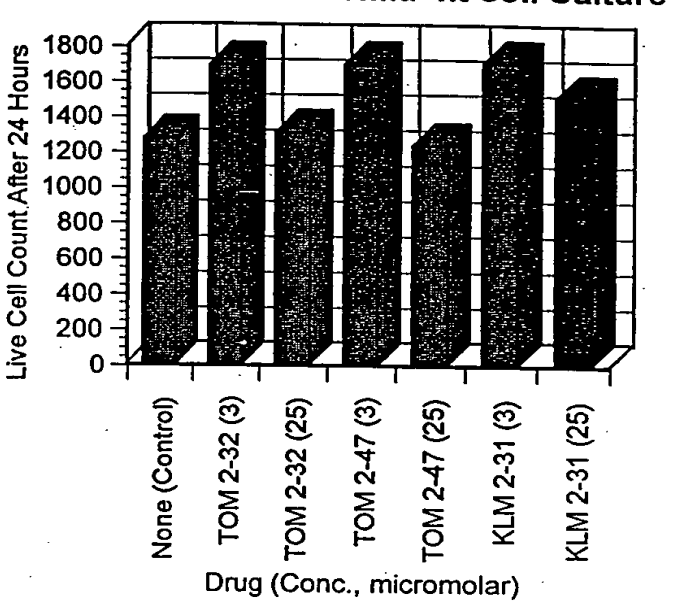
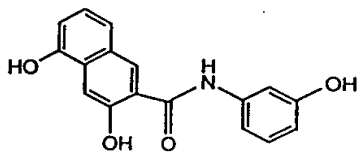
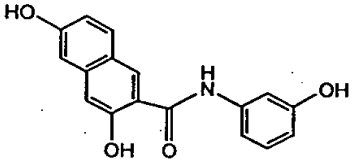


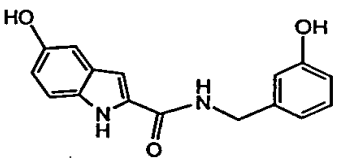
FIGURE 15C



TOM 2-32



TOM 2-47



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